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Intrafascial Dissection Significantly Increases Positive Surgical Margin and Biochemical Recurrence Rates after Robotic-Assisted Radical Prostatectomy

Ashkan Mortezavi[a] Thomas Hermanns[a] Hans-Helge Seifert[a] Peter J. Wild[b] Daniel M. Schmid[a] Tullio Sulser[a] Daniel Eberli[a]

[a]Department of Urology and [b]Institute of Surgical Pathology, University Hospital Zürich, University of Zürich, Zürich, Switzerland

Key Words
Prostate cancer · Prostatectomy · Laparoscopic surgery · Robotics · Intrafascial nerve-sparing

Abstract
Introduction: Improved visualization and magnification in robot-assisted laparoscopic radical prostatectomy (RALRP) has tempted many urologists to dissect the neurovascular bundle closer to the prostate following the layers of the pseudo-capsule of the prostate. This might bear a higher risk of decreased tumor control. ***Materials and Methods:*** An analysis of a consecutive series of 186 patients who underwent RALRP at our institution was performed. The outcome of patients with intrafascial nerve-sparing (INS) was compared with the outcome of patients who underwent interfascial, extrafascial or no nerve-sparing (non-INS). ***Results:*** A total of 80 patients (43.0%) received INS. The overall R1 rate was 27.9%. For pT2 tumors the rate of R1 was 33.8% in INS versus 14.8% in non-INS (odds ratio 2.936, 95% confidence interval 1.338–6.443, p = 0.007). Recurrence-free survival was significantly shorter in INS (p = 0.05; hazard ratio 3.791). ***Conclusion:*** The intrafascial dissection technique for RALRP bears a high risk of incomplete resection in localized prostate cancer resulting in unfavorable outcome.

Introduction

The perfect surgical technique for radical prostatectomy (RP) in localized disease should have minimal perioperative morbidity and completely remove the prostate with tumor-negative margins while preserving urinary continence and erectile function. However, attaining the best possible outcome in one might compromise the other. Over the last years, robot-assisted laparoscopic RP (RALRP) has become a well-established procedure for the management of localized prostate cancer with oncologic and functional results comparable to open retropubic RP and laparoscopic RP (LRP) [1–4]. RALRP offers magnification and improved visualization of the surgical site. This might facilitate the exploration of the neurovascular bundles (NVBs) and may allow a more accurate dissection of the fascial layers.

Intrafascial nerve-sparing (INS) is characterized by a preparation close to the prostatic capsule (PC) with the intention to preserve nerve fibers on the lateral surface of the prostate, which are known to play a significant role in neural stimulation to the cavernous tissue [5–7]. Improved potency and continence rates after RP with INS have been reported [8, 9]. However, the close preparation to the prostate might result in an incomplete resection

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Daniel Eberli, MD, PhD
Department of Urology, University Hospital Zürich
University of Zürich, Frauenklinikstrasse 10
CH–8091 Zürich (Switzerland)
Tel. +41 44 255 1111, E-Mail daniel.eberli@usz.ch

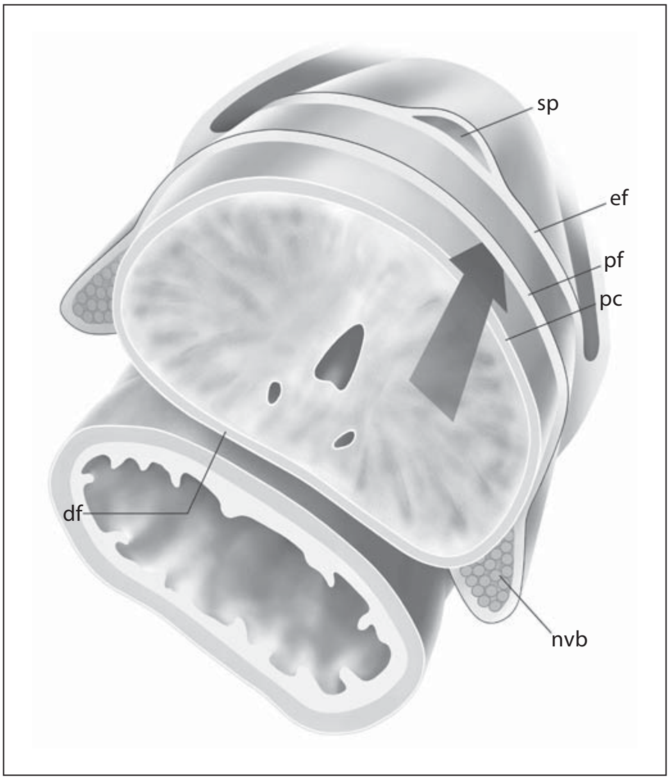

Fig. 1. Three-dimensional schematic depiction of the prostate: anatomic relations of prostate, endopelvic fascia (ef), periprostatic fascia (pf), Denovilliers' fascia (df) and neurovascular bundle (nvb). The arrow indicates the correct layer for intrafascial dissection. sp = Santorini plexus; pc = prostatic capsule.

bearing the risk of a higher rate of positive surgical margins (PSMs). The correlation between PSM and biochemical failure risk is well established [10, 11]. Therefore, the primary goal of RP is complete tumor control with negative margins.

In previous publications, INS was correlated with functional outcome and/or PSM rates with no [9, 12–14] or only short-term oncological outcome [15–17]. In this study we have investigated the influence of INS in RALRP on recurrence-free survival (RFS), PSM rates, location of PSMs, and compared this approach to other techniques of RALRP performed in our institution.

Materials and Methods

Patient Selection

The charts of 186 consecutive patients with prostate cancer who underwent RALRP in the Department of Urology at the University Hospital Zürich between May 2006 and August 2008 were reviewed retrospectively. Only patients operated by surgeons with high caseloads (>50) were included in this study. Peri- and postoperative data including the surgical technique, clinical and pathological data were collected. Operation time included RALRP and lymphadenectomy if performed without an individual time measurement of the two procedures. Patients with intrafascial approach were designated as INS, whereas all other gradations of more lateral preparations were considered as no nerve-sparing (non-INS). No patient received preoperative androgen deprivation. Approval was received from the internal review board.

Surgical Technique

Three senior urologists performed the RALRPs using the three-arm da Vinci System® (Intuitive Surgical Inc., Sunnyvale, Calif., USA). The minimum requirement for the intrafascial approach was a biopsy Gleason score of ≤7 and prostate cancer in less than 50% of the biopsy cores. A unilateral intrafascial dissection of the NVB was performed on the side without positive biopsies or palpable nodules.

The surgical procedure was performed by all three surgeons as follows: If necessary, a bilateral extended pelvic lymphadenectomy was done. Afterwards the ligation of the Santorini plexus was performed. Following dissection of the bladder neck in a straight line down to the pillars, the seminal vesicles were removed completely. If the patient received a nerve-sparing, preparation of the NVB was performed without coagulation in order to avoid thermal damage of the nerve fibers.

For an INS, the lateral release of the NVB started at the posterior surface of the prostate, leaving all lateral layers intact. After incision of the Denonvilliers' fascia (DF) a blunt separation of the prostate and the NVB was performed. The preparation was finished by further dissection directed medially reaching the anterior surface of the prostate. The plane was developed between the PC and its overlaying periprostatic fascia (PF). The correct plane of dissection is recognized when the surface of the prostate is smooth and reflecting. The inter- and extrafascial approaches were performed at the lateral aspect of the prostate laterally to the PF leaving it intact; the dissection began inside/medial of the anterior extension of the DF (interfascial) or outside/lateral of it (extrafascial/non-INS) (fig. 1).

After careful preparation of the apex, the prostate was released and finally the vesicourethral anastomosis was performed with interrupted sutures.

Pathological Evaluation

Tumor stage, Gleason score and surgical margin status were retrieved from the pathological report from the Institute of Clinical Pathology of the University Hospital Zürich. Detailed comprehensive pathologic analysis was performed using standardized whole-mount sections. If tumor cells were detectable at the inked surface, the surgical margins were considered positive. The sites of PSMs (apex, bladder neck, posterior/lateral surface) were assessed.

Oncological Outcome

Clinical follow-up data were collected for all patients. Patients were routinely assessed using a PSA test after 6 weeks, 6 and 12 months, and yearly thereafter. Time to PSA recurrence was selected to assess the oncological outcome (RFS). PSA recurrence was defined as PSA value ≥0.1 ng/ml with consecutive confirmation after reaching a PSA nadir ≤0.1 ng/ml postoperatively. Patients not reaching PSA nadir (<0.1 ng/ml) postoperatively were excluded for RFS analysis because metastatic disease could not be excluded.

Learning Curve

To investigate the relation of surgeon's experience with PSMs, the rate in pT2 disease was calculated for 3-month time segments (fig. 2e). Additionally, to analyze the connection to the nerve-sparing technique, the rate of INS was also calculated over time.

Statistical Analysis

PASW version 18.0 (SPSS, Chicago, Ill., USA) was used for statistical analyses. Contingency table analysis and χ^2 tests were used to assess statistical associations between clinicopathological data and surgical technique for categorical and grouped variables. For comparison of means the independent-samples t test was performed. Kaplan-Meier estimates were computed for RFS and were compared between the two groups using the log-rank test. Patients were censored at the time of first PSA recurrence. A multivariable Cox regression model was adjusted, testing the independent prognostic relevance of the surgical technique. Pearson correlation was used to evaluate the statistical correlation between PSM and INS. All p values ≤0.05 were considered significant.

Results

Descriptive Analysis

A total of 80 patients (43.0%) received a RALRP with INS. 106 patients were operated with a more lateral preparation (non-INS). In INS, 57.5% (n = 46) received nerve-sparing on both sides whereas only 23.6% (n = 25) in non-INS did.

Patients in INS were significantly younger (62.55 vs. 64.86, p = 0.014) and had a lower BMI (25.57 vs. 26.44, p = 0.061). Further, the biopsy Gleason score (70% ≤6 vs. 48% ≤6, p < 0.003) and preoperative PSA (7.16 vs. 11.53, p = 0.001) were significantly lower. For perioperative patient characteristics, see table 1.

Pathologic Evaluation

Gleason score distribution was significantly different between INS and non-INS (38% ≤6 vs. 23.6% ≤6, p = 0.020). Evaluation of the specimen revealed that 152 patients (81.7%) had a pT2 and 34 patients (18.3%) a pT3 tumor. The diagnosis of a pT3 tumor was made in 11.3% of cases in INS and in 23.6% of cases in non-INS (p = 0.023).

Univariate analysis showed that INS was a significant predictive factor for PSMs in pT2 tumors (33.8 vs. 14.8%; odds ratio (OR) 2.936, 95% confidence interval (CI) 1.338–6.443, p = 0.007; table 1) but not for pT3 tumors (OR 0.867, 95% CI 0.187–4.007, p = 0.855). The majority of PSMs in pT2 tumors was found at the apex (44.4%) with no significant difference between the two groups (50 vs. 33.3%, p = 0.389; table 1). For pT3 tumors, the majority of PSMs (62.5%) had a multifocal location (p = 0.209). No difference for PSMs comparing different surgeons and nerve-sparing technique could be observed (data not shown).

Figure 2e represents the percentage of PSMs for pT2 tumors over time. Our data failed to demonstrate a decrease of the PSM rate over the study period of 27 months. A significant positive correlation between PSM rates and percentage of INSs performed was maintained over time (Pearson correlation 0.846, p = 0.004).

Oncological Outcome

Follow-up data were available for 136 of 152 patients (89.4%) in the pT2 cohort and for 34 patients (100%) in the pT3 cohort. Median follow-up of both cohorts was 24 months (range 0–45). Ten patients not reaching nadir (≤0.1 ng/ml) postoperatively were excluded for RFS analysis. Univariate Cox regression analysis (table 2) and Kaplan-Meier analysis (fig. 2a, b) revealed that RALRP with INS as well as PSMs were significantly associated with shorter RFS in pT2 tumors (hazard ratio (HR) 3.791, p = 0.05 and HR 7.045, p = 0.002, respectively). The multivariate analysis for RFS (table 2) showed a HR for INS of 5.363 (p = 0.045, 95% CI 1.039–27.680) and for PSMs of 6.268 (p = 0.006, 95% CI 1.697–23.149), respectively. No such effect could be observed for pT3 tumors (table 2; fig. 2 c, d).

Discussion

Nearly 30 years ago, Walsh and Donker [18] first described a nerve-sparing RP, which increased the acceptance of the operation to patients, referring physicians and surgeons. For many years, the open RP remained the standard for treatment of patients with a localized disease. In an effort to further decrease the morbidity, a minimally invasive surgical approach to treating prostate cancer (i.e. LRP) was first described in 1997 by Schuessler et al. [19]. The introduction of LRP and later RALRP offered additional magnification and improved visualization of the surgical site allowing urologists to rediscover the prostatic anatomy. The better distinction of the fibrous layers made different approaches to these fascial planes possible [8, 20].

A novel surgical technique suggested by Stolzenburg et al. [8] with the goal of improved nerve-sparing was the intrafascial preparation. This technique requires a per-

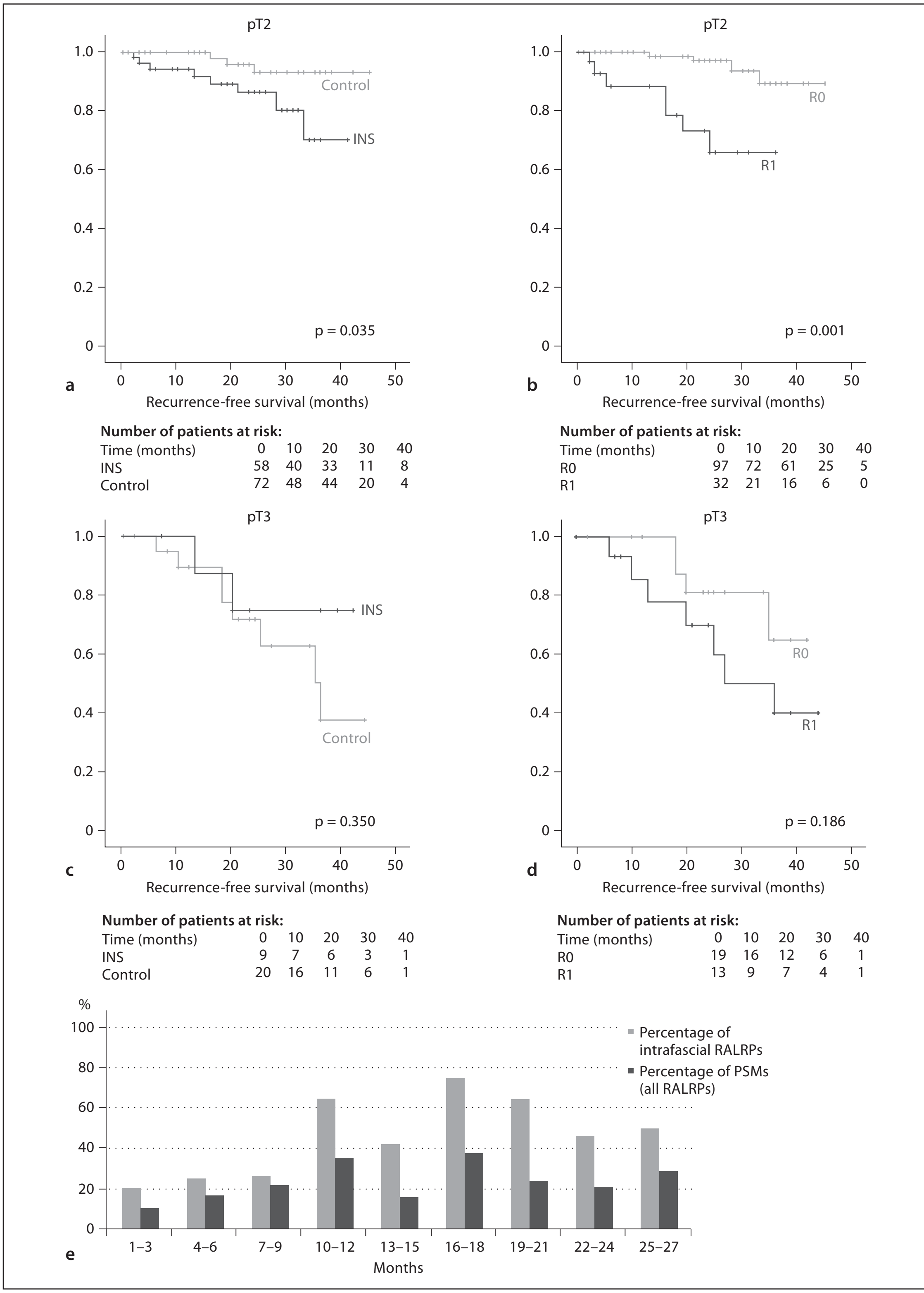

Fig. 2. a–d Kaplan-Meier curves showing RFS of prostate cancer patients with pT2 (**a**, **b**) and pT3 (**c**, **d**) disease who underwent RALRP with INS versus patients with other techniques (**a**, **c**) and with PSM status versus negative surgical margin status (**b**, **d**). **e** Cumulative bar chart representing percentage of intrafascial prostatectomies and percentage of PSMs in pT2 disease subdivided for 3-month time segments starting May 2006.

Table 1. Perioperative patient characteristics and positive surgical margins

	Total cohort (n = 186)	INS: intrafascial (n = 80)	Non-INS: inter-/extrafascial, no nerve-sparing (n = 106)	p*	Test type
Preoperative data					
Age, years	63.87 ± 6.37	62.55 ± 6.82	64.86 ± 5.86	**0.014**	t test
Body mass index, kg/m²	26.06 ± 3.14	25.57 ± 3.16	26.44 ± 3.10	0.061	t test
Preoperative PSA, ng/ml	9.64 ± 8.61	7.16 ± 3.60	11.53 ± 10.64	**0.001**	t test
Gleason biopsy score				**0.003**	χ^2
5–6	107/186 (57.5%)	56/80 (70.0%)	51/106 (48.1%)		
7	67/186 (36.0%)	23/80 (28.7%)	44/106 (41.5%)		
8–10	12/186 (6.5%)	1/80 (1.3%)	11/106 (10.4%)		
Intraoperative data					
Operation time, min	241.76 ± 79.15	213.15 ± 70.49	263.35 ± 78.77	**<0.001**	t test
Estimated blood loss, ml	513.32 ± 466.60	450.50 ± 341.31	558.40 ± 541.39	0.121	t test
Hemoglobin preoperative, g/dl	14.72 ± 1.22	14.73 ± 1.26	14.72 ± 1.19	0.963	t test
Hemoglobin postoperative, g/dl	11.21 ± 1.53	11.16 ± 1.55	11.25 ± 1.53	0.706	t test
Transfusion rate	11/186 (5.9%)	8/80 (10%)	3/106 (2.8%)	**0.041**	χ^2
Postoperative data					
Hospital stay, days	7.49 ± 4.47	6.89 ± 2.70	7.94 ± 5.40	0.111	t test
Complication rate	27/186 (14.5%)	7/80 (8.8%)	20/106 (18.9%)	0.052	χ^2
Gleason score				**0.020**	χ^2
5–6	55/185 (29.7%)	30/79 (38%)	25/106 (23.6%)		
7	103/185 (55.7%)	43/79 (54.4%)	60/106 (56.6%)		
8–10	27/185 (14.6%)	6/79 (7.6%)	21/106 (19.8%)		
pT stage				**0.023**	χ^2
pT2a–c	152/186 (81.7%)	71/80 (88.7%)	81/106 (76.4%)		
pT3ab	34/186 (18.3%)	9/80 (11.3%)	25/106 (23.6%)		
Median follow-up, months (median)	23 (0–45)	23 (1–42)	24 (0–45)		
pT2 tumors					
Positive surgical margins, R1	36/152 (23.8%)	24/71 (33.8%)	12/81 (14.8%)	**0.007**	χ^2
Location of positive surgical margins				0.389	χ^2
Apex	16/36 (44.4%)	12/24 (50%)	4/12 (33.3%)		
Posterior/lateral	10/36 (27.8%)	7/24 (29.2%)	3/12 (25.0%)		
Bladder neck	4/36 (11.1%)	1/24 (4.2%)	3/12 (25.0%)		
Multifocal	6/36 (16.7%)	4/24 (16.7%)	2/12 (16.7%)		
pT3 tumors					
Positive surgical margins, R1	16/34 (47.1%)	4/9 (44.4%)	12/25 (48.0%)	0.855	χ^2
Location of positive surgical margins				0.209	χ^2
Apex	2/16 (12.5%)	1/4 (25%)	1/12 (8.3%)		
Posterior/lateral	3/16 (18.8%)	2/4 (50%)	1/12 (8.3%)		
Bladder neck	1/16 (6.3%)	0/4 (0%)	1/12 (8.3%)		
Multifocal	10/16 (62.5%)	1/4 (25%)	9/12 (75%)		

Data are means ± SD or numbers unless otherwise mentioned. * p values ≤0.05 are marked in bold.

fect exposure of the anatomical layers surrounding the prostate to remove the prostate without periprostatic tissue. Three fibrous layers surrounding the prostate can be individualized during RALRP [21]. The endopelvic fascia, the PF and the DF cover the prostate gland and form the periprostatic environment (fig. 1). INS is considered a dissection that follows a plane on the PC and runs under the PF. It also remains anterior to the DF. The interfascial approach, in contrast, is performed outside or laterally to the PF at the antero- and posterolateral aspects of the prostate. The PF remains intact and is removed with the prostate [22]. In the extrafascial approach the dissection

Table 2. Uni- and multivariate Cox regression analysis in pT2 and pT3

Variable	Characteristics	Recurrence-free survival		
		HR	95% CI	p
Univariate Cox regression analysis, pT2				
Age		1.001	0.915–1.094	0.990
Gleason score (grouped)	5–6 vs. 7 vs. 8–10	0.314	0.214–1.683	0.332
Surgical margin status	negative vs. positive	7.045	2.058–24.123	**0.002**
Preoperative PSA level (grouped)	<10 vs. 10 ng/ml	2.430	0.685–8.620	0.169
Surgical technique	INS vs. other	3.791	1.001–14.356	**0.050**
Multivariate Cox regression analysis, pT2				
Age		1.051	0.948–1.164	0.347
Gleason score (grouped)	5–6 vs. 7 vs. 8–10	0.618	0.189–2.018	0.425
Surgical margin status	negative vs. positive	6.268	1.697–23.149	**0.006**
Preoperative PSA level (grouped)	<10 vs. 10 ng/ml	3.115	0.834–11.636	0.170
Surgical technique	INS vs. other	5.363	1.039–27.680	**0.045**
Univariate Cox regression analysis, pT3				
Age		1.030	0.901–1.178	0.656
Gleason score (grouped)	5–6 vs. 7 vs. 8–10	0.493	0.155–1.574	1.574
Surgical margin status	negative vs. positive	2.735	0.796–9.398	0.101
Preoperative PSA level (grouped)	<10 vs. 10 ng/ml	1.268	0.385–4.174	0.697
Surgical technique	INS vs. other	0.465	0.098–2.199	0.301
Multivariate Cox regression analysis, pT3				
Age		1.069	0.914–1.250	0.405
Gleason score (grouped)	5–6 vs. 7 vs. 8–10	0.458	0.092–2.281	0.340
Surgical margin status	negative vs. positive	1.642	0.438–6.160	0.462
Preoperative PSA level (grouped)	<10 vs. 10 ng/ml	0.864	0.213–3.506	0.838
Surgical technique	INS vs. other	0.462	0.081–2.630	0.384

p values ≤0.05 are marked in bold.

is outside or lateral of the anterior extension of the DF. In this plane a partial or no preservation of the NVB can be performed [23].

The intrafascial approach has the potential to spare more nerve fibers but also increase the risk of higher PSM rates. In the present investigation we found an OR of 2.936 for PSMs and a HR of 3.791 for RFS comparing INS versus non-INS in pT2 disease. Considering the clinical impact of a positive margin status on cancer recurrence [10, 11], the oncological safety of this procedure has to be called into question. The current level of PSM rates for all techniques (pT2 tumors, RALRP) has been reported as 2.5–18% (mean 9.6% [for recent review, see 24]) and for the intrafascial technique (pT2, open RP, LRP, RALRP) 4.5–21.9% [9, 12–17, 25]. In this context, our PSM rate in pT2 disease for INS is surprisingly high with 33.8% while our PSM rate for other techniques is tolerable compared to other initial series described for RALP (14.8% in non-INS, pT2 [24]).

In this research a significant shorter RFS in INS (pT2) could already be demonstrated at a median follow-up of 24 months, clearly showing that the group with better operative baseline parameters (Gleason score in biopsy and preoperative PSA level) had a worse cancer-specific outcome. In both the uni- and multivariate analysis, PSM rate and INS were predictors for biochemical recurrence. Notably, the well-established long-term predictors Gleason score and preoperative PSA did not remain significant in the uni- and multivariate analysis after a 2-year follow-up, indicating the surgical technique and margin status have a higher impact on early RFS. Furthermore, no differences in both groups for PSM and RFS rates could be observed in pT3 disease (44.4% in INS vs. 48.0% in non-INS, p = 0.855), suggesting that the surgical technique has a limited impact for tumors with extraprostatic extension.

As commonly observed, in this series most of the positive margins in pT2 disease were located at the prostatic apex, where the different fascial layers become less distinctive and are often mixed with skeletal muscle of the sphincter [26, 27]. This distribution of PSMs is even more prominent if INS is performed. Our data indicate that during the preparation of the NVB the intrafascial preparation guides the surgeon too close to the prostate tissue further increasing the PSM at the apex. In pT3 disease mostly a multifocal affection of the surgical margins could be observed, indicating the more aggressive character of these tumors.

As for many novel techniques, evaluation of a learning curve has to be taken in account. For RALRP, different groups have reported short learning curves [28]. In the present series, no decline of the PSM rate could be observed over the 27 months (fig. 2e). We actually found a significant correlation between percentage of INS surgery and percentage of PSMs over time. In our hands, the intrafascial technique introduces a systematic error with a consistently lower tumor control.

A limitation of this investigation is the general shortcoming of the pathologic TNM staging. In this study, patients with pT3 disease were more frequent in non-INS. This might be due to patient selection (high-risk patients received more often a non-INS). But one has to take in account that the diagnosis of pT3 prostate cancer can only be made with PF attached to the prostatic specimen [23]. During INS the PF is preserved which can mislead the pathologist staging a true pT3 tumor as pT2 with PSM [29]. Therefore, unidentified biologically more aggressive pT3 tumors might have shortened the RFS in INS [29]. Further limitation is the lack of randomization due to the retrospective manner of this study. Nevertheless, in spite of better prognostic parameters, the outcome was reversely poor in the INS group.

The intrafascial technique to preserve the NVB is technically feasible but in our hands is correlated with significantly higher PSM rates and early biochemical failure without an improvement over the study period. We believe that a possible gain in erectile and continence recovery does not justify the significantly decreased tumor control. Therefore, we recommend abandoning this technique for the preparation of the NVB in RALRP in favor of a more lateral approach.

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